Original paper

Gluten-free diet changes the lipid profile of children and adolescents with coeliac condition

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Abstract

Introduction: the gluten-free diet is the only treatment for coeliac disease. Gluten-free products contain a higher percentage of carbohydrates and saturated lipids, which can lead to long-term metabolic problems. The aim of this study is to analyse the lipid profile of children and adolescents under 18 years of age after their diagnosis of coeliac disease and its modification after starting treatment.

Material and methods: to this end, a retrospective observational study of children diagnosed with coeliac disease without other comorbidity and following a strict gluten-free diet was carried out. Lipid profiles were collected and compared at disease onset, one year and six years after the start of the gluten-free diet.

Results: twenty-four paediatric patients were included and an increase in total cholesterol levels and a decrease in triglyceride levels were observed, both with statistical significance ($p<0.05$).

Conclusions: we believe it is important to analyse the nutritional profile of paediatric coeliac patients at the time of diagnosis of the disease as well as during the follow-up of their gluten-free diet, in order to detect metabolic and/or nutritional problems at an early stage, thus preventing the development of consequences that may appear as early as infancy.

Key words:
- Coeliac disease
- Gluten
- Lipid profile

La dieta sin gluten cambia el perfil lipídico de los niños y adolescentes celiacos

Resumen

Introducción: la dieta sin gluten es el único tratamiento de la enfermedad celíaca. Los productos sin gluten contienen un mayor porcentaje de carbohidratos y lípidos saturados, lo que puede producir problemas metabólicos a largo plazo. Dado que la arteriosclerosis es la principal causa de morbimortalidad en los países desarrollados, el objetivo de este trabajo es analizar el perfil lipídico de niños y adolescentes por debajo de los 18 años tras su diagnóstico como celíacos y su modificación después de iniciar el tratamiento.

Material y métodos: se llevó a cabo un estudio observacional retrospectivo de niños diagnosticados de enfermedad celíaca sin otra comorbilidad que seguían una dieta sin gluten estricta. Se recogieron y compararon los perfiles lipídicos al debut de la enfermedad, al año y a los 6 años del inicio de la dieta sin gluten.

Resultados: en el estudio se incluyó a 24 pacientes pediátricos. Se objetivó un ascenso de los niveles de colesterol total y un descenso de los niveles de triglicéridos, ambos con significación estadística (p <0,05).

Conclusiones: creemos importante analizar el perfil nutricional de los pacientes celíacos pediátricos al diagnóstico de la enfermedad, así como en el seguimiento de su dieta sin gluten, para poder detectar problemas metabólicos y/o nutricionales de manera precoz, atajando el desarrollo de consecuencias que pueden dar la cara ya desde el periodo infantil.

Palabras clave:
- Enfermedad celíaca
- Gluten
- Lípidos

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INTRODUCTION

Untreated coeliac disease (CD) may be associated with the development of autoimmune diseases, metabolic bone diseases, infertility, recurrent miscarriage and neurological and psychiatric disorders. If the gluten-free diet (GFD) is strictly followed, 10 years after diagnosis the risk of oncological and autoimmune disease is similar to that of the general population.[1]

However, the gluten-free diet does not only have beneficial effects. A study published in 2017 comparing the dietary intake of 98 patients with CD aged 10-23 years to 98 healthy controls without CD matched for age, sex and body mass index found that patients with CD under a GFD consumed more total fat, added sugars, protein and sugary drinks compared to healthy controls. Both groups followed an unbalanced diet characterised by a low fibre intake and a higher than recommended sodium intake, and also failed to adhere to current recommendations for optimal micronutrient intake. However, the intake of folic acid, calcium, iron and magnesium was lower in cases compared to controls.[2] Similarly, a study conducted by Elliott confirmed that approximately 80% of gluten-free products specifically targeted at children have a high sugar content.[3]

On the other hand, gluten-free products also contain a higher percentage of saturated fats[4,5] in an attempt to address manufacturing challenges (preserving the texture, volume or even taste) associated with the absence of gluten. This is the reason why individuals in treatment for coeliac disease are at increased risk of overweight and obesity. They are also more likely to develop metabolic complications due to an increase in visceral fat, in addition to an increased mortality from cardiovascular disease associated with the vascular damage caused by chronic inflammation.[4,5]

Dyslipidaemia is a term that refers to changes in blood concentrations of lipoproteins (cholesterol, triglycerides and apoproteins). Their levels are determined by genetic and environmental factors, such as diet and physical activity, among others. The relationship between dyslipidaemia and the development and progression of atherosclerosis is well known. This process begins in childhood with the appearance of fatty streaks in the arterial wall, can worsen in adolescence with the development of atheromatous plaques and manifests clinically in adulthood as arterial obstruction.[6]

Given that atherosclerosis is the leading cause of morbidity and mortality in developed countries,[6] the aim of our study was to analyse the lipid profile of children and adolescents aged less than 18 years after the diagnosis of coeliac disease and the followup of the GFD in order to determine the risk that these patients may experience, as it could become a powerful tool for early prevention in this population.

MATERIAL AND METHODS

We carried out a retrospective and descriptive observational study in a public primary care centre in Spain of all children under 18 years diagnosed with coeliac disease. The objectives of the study were:

- Defining the lipid profile of children with newly diagnosed CD.
- To assess the impact of the GFD on cholesterol and triglyceride levels in paediatric patients with CD in the short and long term.

The sample included coeliac patients in the caseload of the primary care centre who followed a GFD. We included patients who had onset of coeliac disease before age 18 years and who did not have any other diseases. We excluded patients whose health records were not completely digitalised, as this would make it difficult to access information on the diagnosis and the early years of the disease.

We reviewed the full health records of the patients included in the sample after obtaining informed consent from the patients or their legal guardians. We collected data on the following variables: age at onset, cholesterol and triglyceride levels at onset, cholesterol and triglyceride levels 1 year and 6

years after initiation of the GFD and anti-tissue transglutaminase antibody levels as an indirect measure of adherence to the diet. We scheduled the second set of monitoring tests at age 6 years because it was the longest duration of followup that could be achieved for all patients. All samples for testing were collected after a fasting period of at least 8 hours.

We defined hypercholesterolaemia and hypertriglyceridaemia as concentrations of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c) and triglycerides (TG) above the 95th percentile (P95): TC ≥200 mg/dl, LDL-c ≥130 mg/dl and TG ≥130 mg/dl. We also took into account the reference range for TC (170-199 mg/dl), LDL-c (110-129 mg/dl) and TG (90-130 mg/dl). The ranges of values applied for high-density lipoprotein cholesterol (HDL-c) were <40 mg/dl for abnormal values and 40-45 mg/dl for borderline values.

For the statistical analysis, we analysed distributions using the Shapiro-Wilk test. Continuous quantitative variables were expressed as median and interquartile range (IQR) [P25-P75] or as mean ± standard deviation (SD) based on whether the data followed a normal distribution, and qualitative variables were expressed as absolute frequency (percentage %). We measured the association between quantitative variables by means of the Student *t* test for paired samples or the Wilcoxon test based on the shape of the distribution. All tests were bilateral and statistical significance was established at less than 5% was established. The analysis was performed with the SPSS software.

RESULTS

The sample included 24 patients. Seventy-five percent were female. The median age at diagnosis was 3 years (IQR 2-10 years). **Table 1** summarises the results of the descriptive analysis of the lipid profile at disease onset and of the follow-up testing at 1 and 6 years of the GFD. Only 17%[4] of children tested positive for antibodies in the control at 1 year, but had a normal lipid profile. At 6 years, 100% tested negative for the antibodies.

In our laboratory, LDL-C and LDL-C levels are only measured if the TC is higher than the upper limit of normal, so we only have results for 2 patients at the time of onset, 4 at one year of the GFD and 5 at six years of the GFD (**Table 2**).

When we compared baseline TC and TG levels with the results of follow-up tests at 1 and 6 years, we found that TC levels had increased and TG levels decreased, differences that were statistically significant (**Table 3**). We were unable to compare HDL-C and LDL-C levels as they were not measured in every patient. Only one patient in the sample had sustained elevation of TC throughout the study period, with an increase in LDL-C (55-58-58 mg/dL) and a decrease in LDL-C (141-132-132 mg/dL) over the followup.

Another patient who had hypercholesterolaemia at baseline, with an LDL-C level in the normal range and a LDL-C in the borderline range, had normal TC values in subsequent time points. Three patients started with elevated TC levels at 1 year of the GFD, but the elevation was sustained through

Table 1. Descriptive analysis of lipid profiles

	TC at onset	TG at onset	TC at 1 year of GFD	TG at 1 year of GFD	CT at 6 years of GFD	TG at 6 years of GFD
Mean ± SD or Me (IQR) (mg/dl)	147 (SD 27)	81 (IQR 58-128)	161 (SD 31)	68 (IQR 50-74)	164 (SD 34)	60 (IQR 50-69)
% of patients with borderline values (P75-P95)	8	17	17	13	29	13
% of patients with elevated values (> P95)	8	25	17	4	21	0

GFD: gluten-free diet; **IQR:** interquartile range; **Me:** median; **P:** percentile; **TC:** total cholesterol; **TG**: triglycerides; **SD:** standard deviation.

Table 2. Descriptive analysis of HDL- and LDL-cholesterol levels in patients with elevated TC

	HDL-C at onset (n = 2)	LDL-C at onset (n = 2)	HDL-C at 1 year of GFD (n = 4)	LDL-C at 1 year of GFD (n = 4)	HDL-C at 6 years of GFD (n = 5)	LDL-C at 6 years of GFD (n = 5)
Median and IQR (mg/dl)	58 (IQR 55-58)	134 (IQR 127-134)	60 (IQR 56-60)	133 (IQR 133-137)	77 (IQR 57-77)	130 (IQR 107-130)
% of patients with borderline values (P75-P95)	0	50	0	0	0	20
% of patients with elevated values (> P95)	0	50	0	100	0	60

GFD, gluten-free diet; **HDL-C,** high-density lipoprotein cholesterol; **IQR,** interquartile range; **LDL-C,** low-density lipoprotein cholesterol; **P,** percentile.

Table 3. Comparison of lipid levels at baseline and after initiation of the gluten-free diet.

	TC from baseline to 1 year of GFD	TC from baseline to 6 years of GFD	TG from baseline to 1 year of GFD	TG from baseline to 6 years of GFD
% increase or decrease	9.5% increase	11.5% increase	16.5% decrease	26% decrease
***p* value**	0.043	0.036	0.028	0.014

GFD: gluten-free diet; **TC:** total cholesterol; **TG**: triglycerides.

the end of followup in only two; in these patients, the HDL-C levels remained within the normal range and the LDL-C levels decreased (HDL-C 63-56 and 64-78 mg/dL; LDL-C 133-130 and 134-114 mg/dL). Only one patient developed hypercholesterolaemia 6 years after initiation of the GFD, and his HDL-C and LDL-C levels were normal.

DISCUSSION

The main finding of this study is that following a gluten-free diet is associated with changes in the lipid profile, with an increase in TC levels and a decrease in TG levels.

Several studies in the literature have analysed lipid levels before and after the initiation of a GFD in adults with coeliac disease.[7] In a retrospective cohort study, 185 adults with CD were tested at diagnosis, 1 year after initiation of the diet and once a year thereafter in the annual follow-up visit (median followup 7 years). The highest prevalence of metabolic disorders overall was found after 5-10 years of followup, exceeding 40% at 6 years, specifically. In our patients, we found the highest prevalence of hypercholesterolaemia (21%) at 6 years of followup. In contrast with our findings, the authors of that study found a significant reduction in HDL-C and TG levels in the elevated range after GFD, although the latter was not statistically significant.[8] On the other hand, a cross-sectional study aimed at establishing the prevalence of type 2 diabetes and metabolic syndrome conducted in 840 patients with CD compared to age-, sex- and ethnicity-matched controls found a significantly lower incidence of dyslipidaemia in cases compared to controls, with a mean duration of the GFD in the case group of 7 years.[9] Tortora *et al.*[10] assessed for the presence of diagnostic criteria for metabolic syndrome (increased abdominal circumference, hypertension, low HDL levels, high TG levels, fasting hyperglycaemia) in 98 adults with newly diagnosed CD at diagnosis and at one year of the GFD. There was a 27.5% increase in the diagnosis of metabolic syndrome, but there were no significant differences in disorders of lipid metabolism between the two timepoints.[10]

A systematic review published in 2018 included 27 cohort studies and randomised controlled trials in

adults, of which only one had a control group, which precluded conducting a meta-analysis of the results. The overall quality of the studies was low: 6 studies reported TC values, with 3 describing a significant increase. Of the 6 studies that reported HDL-C levels, 5 described a significant increase, which was more consistent with our findings. Of the 4 studies that reported LDL-C levels, 3 described nonsignificant changes and 1 a significant increase. Of the 5 studies that reported TG levels, 4 described nonsignificant changes and 1 a significant decrease.[11]

Few studies have been conducted in the paediatric population. Norsa *et al*.[12] conducted a multicentre, cross-sectional study in 114 children aged less than 18 years with a diagnosis of CD (and no comorbidities) who were in serologic remission and had been on a GFD for at least 1 year. The aim was to describe risk factors for cardiovascular disease in this population. The most frequent risk factors identified in the study were elevated fasting TG levels (34.8%), high blood pressure (29.4%) and elevated LDL-C values (24.1%). The main limitation of this study was that lipid profile data predating the CD diagnosis were available for only 50% of the enrolled patients. In any case, LDL-cholesterol values were normal in 63% of the patients in the cohort, borderline in 30% and elevated in 7% after at least one year of the GFD. When it came to our study, as noted above, we were unable to perform an inferential analysis of LDL-C levels due to the small number of patients with a complete lipid profile, but the data also showed an increasing trend in this lipoprotein one year after the GFD, although the values had decrease at 6 years. In line with our findings, the authors also reported significant increase in both TC and HDL-C levels in patients under a GFD. Lastly, the authors concluded that, although the elevation of LDL-C could increase cardiovascular risk, the concomitant increase in HDL-C could be cardioprotective, so further research with assessment of other markers is needed to determine whether a GFD is detrimental in this respect.[12]

Pes GM *et al*.[13] introduced a novel concept in the field. They conducted a retrospective study in 52 adult patients with CD and without dyslipidaemia who had been on the GFD for 2 years and divided them into two subgroups based on whether the baseline LDL-C level was above or below the target value of 100 mg/dl. Thus, they analysed lipid levels before and after the GFD, and found no significant differences. However, LDL-C levels increased by 20% and decreased by 10% in the subgroups of patients with baseline values below or above 100 mg/dl, respectively. In addition, TC levels exhibited a similar trend, while HDL-C and TG levels increased in both subgroups. Thus, the authors concluded that it is likely that in newly diagnosed patients with low cholesterol levels, a GFD may results in an increase in cholesterol levels through increased intestinal absorption. However, in the subset of patients whose cholesterol level is elevated at baseline, the diet may achieve a reduction in cholesterol even before the effects of increased intestinal absorption become apparent.[13] In our study, we were unable to analyse these subgroups because we did not have LDL-C values for all the patients. In addition, if we had established subgroups based on TC values, the size (n) of one group would been of 4 patients and the size of the other group of 20 patients, too large a difference to obtain reliable results.

There are limitations to our study. The small sample size and the lack of a comparison group may limit the validity of the results. These limitations are present in many of the studies on the subject, which would explain the substantial heterogeneity of the reported findings. It is also important to bear in mind that the metabolic profile of coeliac patients, and, more broadly, of each individual, is influenced by other factors in addition to diet, such as genetics, lifestyle and physical activity. Thus, we believe that future studies should include a dietary and physical activity survey, in addition to the relevant laboratory tests.

CONCLUSION

Our findings suggest that the gluten-free diet may carry a risk of lipid profile abnormalities in paediatric patients with CD, so further research on the subject is needed in the paediatric population, including trials with standardised protocols capable of producing representative data that can be generalised. It is important to carry out detailed assessments of nutritional status in children and adolescents with CD at the time of diagnosis and during the followup to allow early detection of any metabolic or nutritional abnormalities and prevention of complications that can develop starting in childhood.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare in relation to the preparation and publication of this article.

AUTHORSHIP

All authors contributed equally to the writing of the published manuscript.

ABBREVIATIONS

CD: coeliac disease • **GFD:** gluten-free diet • **HDL-C:** high-density lipoprotein cholesterol • **IQR:** interquartile range • **LDL-C:** low-density lipoprotein cholesterol • **Me:** median • **P:** percentile • **TC:** total cholesterol • **TG:** triglycerides • **SD:** standard deviation.

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